

## AN IMPROVED AND SCALABLE METHOD DEVELOPED FOR THE SYNTHESIS OF 2-[4-[(4-CHLOROPHENYL) PHENYL METHYL]-1-PIPERAZINYL] ETHANOL, A KEY INTERMEDIATE FOR CETIRIZINE WHICH IS ANTIALLERGIC DRUG

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### ABSTRACT

An improved and scalable method developed for the synthesis of 2-[4-[(4-chlorophenyl) phenyl methyl]-1-piperazinyl] ethanol, a key intermediate for Cetirizine which is antiallergic drug, Starting from commercially available 4-Chlorobenzhydryl piperazine and 2- Chloro ethanol in presence of base Di isopropyl Ethyl Amine and sodium Iodide as a catalyst the method is easy, inexpensive and reproducible and the process is clean and operationally simple.

**KEYWORD:** 2-[4-[(4-Chlorophenyl) Phenyl Methyl]-1-Piperazinyl] Ethanol, Sodium Iodide, Solvent Free Reaction, Antiallergic Drug Cetirizine

### INTRODUCTION

Cetirizine(**Figure 1**): 2-[4-[(4-chlorophenyl) phenyl methyl]-1-piperazinyl] ethoxy] Acetic acid and its salts are well Established drug for the the treatment of allergic syndromes such as chronic and acute allergic rhinitis allergic conjunctivitis pruritus and urticaria The compound Of (Figure 1) is prepared by reacting 4-Chlorobenzhydryl piperazine<sup>1</sup> with 2- Chloro ethanol<sup>2</sup> to form 2-[4-[(4-chlorophenyl) phenyl methyl]-1-piperazinyl] ethanol<sup>3</sup> converting that product to 2-[4-[(4-chlorophenyl) phenyl methyl]-1-piperazinyl] ethoxy] Acetic acid and converting the latter to 2-[4-[(4-chlorophenyl) phenyl methyl]-1-piperazinyl] ethoxy] Acetic acid mono hydrochloride.

2-[4-[(4-chlorophenyl) phenyl methyl]-1-piperazinyl] ethanol<sup>3</sup> is the key intermediate for the preparation of Cetirizine. The preparation of 2-[4-[(4-chlorophenyl) phenyl methyl]-1-piperazinyl] ethanol<sup>3</sup> which involves the reaction of reacting 4-Chlorobenzhydryl piperazine<sup>1</sup> with 2- Chloro ethanol<sup>2</sup> gave the 2-[4-[(4-chlorophenyl) phenyl methyl]-1-piperazinyl] ethanol<sup>3</sup>.

The Reaction is generally carried out by using aromatic solvents such as Toluene Xylene, etc. preferably Toluene, suitable organic base such as tertiary organic base like triethyl amine or Organic base like Sodium Carbonate.

The Reaction typically performed at reflux Temperature by using solvent Toluene, 2. 2 fold triethyl amine and 1.78 fold 2-Chloro Ethanol. We encounters some difficulties while preparing the: 2-[4-[(4-chlorophenyl) phenyl methyl]-1-piperazinyl] ethanol<sup>3</sup> by the reported method, we observed that the reaction was performed at reflux temperature at 110to120°C, it took 20 to25 Hrs for completion, and various impurities formation observes which reduce yield.

### Experimental Section

Di isopropyl Ethyl Amine and 2-chloro ethanol used were of LR grade TLC was performed on percolated silica gel plates which were visualised using UV light.

HPLC chromatogram were measured with the alliance HPLC device with photo iodide array (PDA) detector,

stationary phase Zorbax SB phenyl, 4.6 mm X250mm, 5 $\mu$ m was use for the analysis; column temperature was 40°C the mobile phase A comprised mixture of buffer solution pH 7.0 and methanol in proportion (80:20 v/v) and mobile phase B comprised of mixture of methanol and buffer solution pH 7.0 in proportion (80:20 v/v). The buffer solution was 0.05 M KH<sub>2</sub>PO<sub>4</sub> solution adjusted to pH 7.0 with potassium hydroxide Gradient mode with the flow rate of mobile phase 1.5 ml/min was used run time 40 min detection at the wavelength 225 nm was used. Methanol was used as a solvent for the preparation of samples; 20 $\mu$ l of solution was used for the injection. The gradient HPLC method was used for checking analysis of compound 1, 2 and 3.

### Preparation of 2-[4-[(4-Chlorophenyl) Phenyl Methyl]-1-Piperazinyl] Ethanol

4-Chlorobenzhydryl piperazine<sup>1</sup> (10gm, 0.0348 mol) and 2- Chloro ethanol <sup>2</sup> (3.35gm, 0.0417 mol) added in four necked round bottom flask equipped with condenser stopper and thermometer pocket in presence of sodium Iodide (0.13 gm, 0.0086) and Di isopropyl ethyl amine (5.7 gm, 0.044mol) the reaction mass is heated and maintained for 6 to 8 Hrs at 110°C to 115°C to form 2-[4-[(4-chlorophenyl) phenyl methyl]-1-piperazinyl] ethanol The completion of reaction was monitored by HPLC, after completion of the reaction reaction mixture was cool to 60°C to 65°C Toluene 500 ml was added and washed with (200mlX2) water, Toluene was distilled under Vacuum to get oil mass yield 90% and HPLC purity 95%.

## RESULTS AND DISCUSSIONS

As a part of ongoing research program on improving synthetic process for pharmaceutically important intermediate 2-[4-[(4-chlorophenyl) phenyl methyl]-1-piperazinyl] ethanol<sup>3</sup>, we report herein the improved and scalable process of 2-[4-[(4-chlorophenyl) phenyl methyl]-1-piperazinyl] ethanol<sup>3</sup> key intermediate for Cetirizine, The reaction is solvent free, reaction completed in 6 to 8 Hrs, less impurities and high purity obtained. In the preliminary study the reaction of 4-Chlorobenzhydryl piperazine<sup>1</sup> with 2- Chloro ethanol<sup>2</sup> was tested in different conditions such as different solvent Volumes addition of sodium Iodide as catalyst use of different base (Table 1)

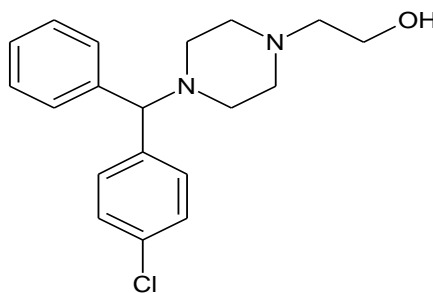
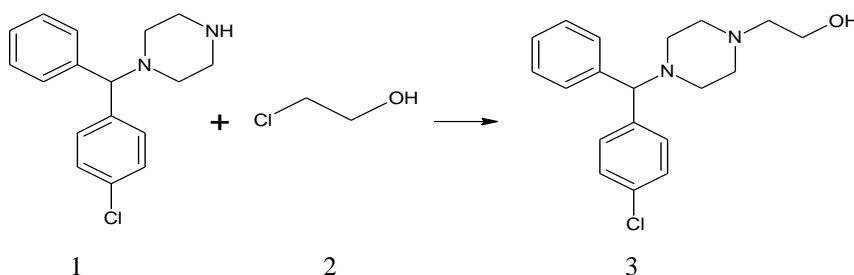


Figure 1



Scheme I

**Table 1: The Reaction of 4-Chlorobenzhydryl Piperazine with 2- Chloro Ethanol in the Presence of Various Condition**

Sr No	Toluene Volume	Base	Sodium Iodide	Reaction Time
1	5.0V	Triethyl Amine	-	21 Hrs
2	5.0V	Triethyl Amine	0.025M	18 Hrs
3	5.0V	Di isopropyl Ethyl Amine	-	15 Hrs
4	5.0V	Di isopropyl Ethyl Amine	0.025M	12 Hrs
5	2.0V	Di isopropyl Ethyl Amine	0.025M	10Hrs
6	0.0V	Di isopropyl Ethyl Amine	0.025M	8hrs

It was found that solvent free condition is superior to all the conditions. The reaction is solvent free which increases batch capacity on commercial Scale, reaction completed in 6 to 8 Hrs which increases production rate, less impurities and high yield obtained which reduce final material cost. The impurities form in this step carry forward in next step to get highly pure Cetirizine it requires additional purification.

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